

# **NUTRITIONAL AND PHARMACOLOGICAL MODULATION OF THE METABOLIC RESPONSE OF SEVERELY BURNED PATIENTS: REVIEW OF THE LITERATURE (part 1\*)**

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**SUMMARY.** Severe burn patients are some of the most challenging critically ill patients, with an extreme state of physiological stress and an overwhelming systemic metabolic response. Increased energy expenditure to cope with this insult necessitates mobilization of large amounts of substrate from fat stores and active muscle for repair and fuel, leading to catabolism. The hypermetabolic response can last for as long as nine months to one year after injury and is associated with impaired wound healing, increased infection risks, erosion of lean body mass, hampered rehabilitation, and delayed reintegration of burn survivors into society. Reversal of the hypermetabolic response by manipulating the patient's physiological and biochemical environment through the administration of specific nutrients, growth factors, or other agents, often in pharmacological doses, is emerging as an essential component of the state of the art in severe burn management. Early enteral nutritional support, control of hyperglycaemia, blockade of catecholamine response, and use of anabolic steroids have all been proposed to attenuate hypermetabolism or to blunt catabolism associated with severe burn injury. The present study is a literature review of the proposed nutritional and metabolic therapeutic measures in order to determine evidence-based best practice. Unfortunately, the present state of our knowledge does not allow the formulation of clear-cut guidelines. Only general trends can be outlined which will certainly have some practical applications but above all will dictate future research in the field.

## **Introduction**

Our understanding of the metabolic changes associated with starvation, stress, and sepsis has deepened over the past 20 to 30 years, and along with this came a greater appreciation for the importance of timing, composition, and route of administration of nutritional support to the trauma patient.<sup>1</sup> Severe burn patients are some of the most challenging critically ill patients with an extreme state of physiological stress.<sup>2-4</sup> Severe burn injuries produce a hypermetabolic response characterized by protein and lipid catabolism, total body protein loss, muscle wasting, peripheral insulin resistance, increased energy expenditure, and stimulated synthesis of acute phase proteins, mainly in the liver as well as in the intestinal mucosa.<sup>4,6</sup> No other single insult results in such an accelerated rate of tissue catabolism, loss of lean body mass, and depletion of energy and protein reserves.<sup>3</sup> Severely burned patients may have multiple-system organ failure with life-threatening

complications requiring a complex interaction of surgical, medical, and critical care and rehabilitation approaches for management.<sup>2</sup>

Treatment of patients with extensive burns remains a tremendous challenge.<sup>4</sup> Control of wound sepsis, decreased hospital stay, and increased survival have been the result of early burn wound excision and wound closure,<sup>7-9</sup> however, and many problems faced by the burn patient remain unsolved, including control and treatment of the hypermetabolic response, which can be extreme.<sup>4,5,10-12</sup> Extensive thermal injury is followed by a severe systemic metabolic response that consists of an early "ebb" phase and a later "flow" phase.<sup>13-18</sup> The "ebb" phase lasts for two to three days and is characterized by a decreased cardiac output and metabolic rate. The "flow" phase begins on day 5 after injury and is characterized by a hyperdynamic circulation and an elevated hypermetabolic rate.<sup>13-15</sup> A significant proportion of the mortality and morbidity of severe burns is attributable to this ensuing hypermetabolic response, re-

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\* Part 2 will be published in the next issue of the journal.

portedly due to increased levels of catecholamines, glucagon, and cortisol.<sup>3,14,19</sup> Increased body temperatures, cool environmental temperatures, extent and depth of burn wounds, evaporative losses from burn wounds, and infectious complications also contribute to the rise in the metabolic rate.<sup>3,19</sup> The increased energy expenditure to cope with this insult necessitates mobilization of large amounts of substrate from fat stores and active muscle for repair and fuel, leading to catabolism. Hyperpyrexia associated with this response adds to the cost as well.<sup>16</sup> The hypermetabolic response can last for as long as nine months to one year after injury and is associated with impaired wound healing, increased infection risks, erosion of lean body mass, hampered rehabilitation, and delayed reintegration of burn survivors into society.<sup>13-15</sup>

Burns being the most hypermetabolic of all surgical diseases, it is natural that appropriate nutrition forms the basis of modern burn care and, concurrently, much of the improvement in burn mortality during the last quarter century has come in conjunction with improved nutrition.<sup>18</sup> Post-burn hypermetabolism can lead rapidly to deleterious consequences if adequate nutritional support is not provided.<sup>3</sup> It is obvious now that nutrition is an integral, though often neglected, component of the care of the critically injured patient.<sup>1</sup> Unfortunately, despite critical advances in our understanding of the pathophysiology of burn injury and major therapeutic modifications over the last three decades that have led to improved survival rates, and although providing nutrition has been clearly recognized as essential in the successful management of severely burned patients, the estimation of burn patients' exact nutritional needs is still a difficult task, and the most appropriate therapeutic regimen to overcome the metabolic response following severe burn injury remains a controversial and unresolved issue.<sup>4,20</sup>

The length of starvation the body can tolerate with negative effects and how long fasting can be tolerated by critically ill patients remains a fundamental question, and probably depends on the severity of the illness or injury.<sup>20</sup> It also remains unknown whether the timing of initiating feeding has any beneficial impact on the metabolic rate.<sup>21</sup> Whether the cut-off of tolerance for introducing feeding is 24 h or more is also as yet undefined and still awaits a prospective trial. There is no real comparative study assessing this question, although a few studies show that standard care (no feeding) is associated with poor outcome compared with feeding (<http://www.evidencebased.net>).<sup>20</sup> However, if the timing of feeding has no impact on the metabolic rate, then perhaps other factors, such as access and associated risks of feeding, should be dominant in determining the nutritional support regimen for these patients.<sup>21</sup>

Our capacity to measure the relevant metabolic/physiological indicators, however, is limited, and energy bal-

ance may be negative over a given period without detectable side effects.<sup>20</sup> Moreover, the available prediction equations of energy balance are usually conceived for resting conditions, making accurate definition of this balance rather difficult in the critically ill.<sup>20,22</sup> Whereas energy intake can be accurately recorded, the measurement of total energy expenditure is problematic, as direct calorimetry or doubly-labelled water, which are the gold standards, are not applicable.<sup>22</sup> At any rate, since severe burn injury is associated with a significant increase in energy expenditure, metabolic demands and nutritional requirements, it is generally believed that provision of an adequate high-calorie nutritional support would lower the incidence of metabolic abnormalities, reduce septic morbidity, improve healing and survival rates, and decrease the length hospital of stay.<sup>23-25</sup>

Any comprehensive management guideline regarding nutritional support in severely burned patients must address six separate issues:

1. The route of nutritional support (total parenteral nutrition vs. total enteral nutrition)
2. Timing of nutritional support (early vs. late)
3. Site of nutritional support (gastric vs. jejunal)
4. Macronutrient formulation (how many calories and what proportion of protein, carbohydrate, and fat?)
5. Type of nutritional support (standard vs. enhanced)
6. Monitoring of nutritional support (which tests and how often?)<sup>1</sup>

Part 1 of this review examines the energy and nutrient requirements of healthy and critically ill patients and the metabolic and hormonal changes following severe burn injury, as well as the assessment of energy and substrate requirements in such patients. Type (hypocaloric or hypercaloric), route, and timing of nutritional support are also reviewed.

### **Energy and nutrient requirements of healthy and critically ill patients**

Total energy requirements matched to satisfy energy expenditure are highly variable, ranging from 1200 kcal/day in a resting, lean subject to over 14,000 kcal/day during a polar expedition. Critical illness naturally adds to the variability.<sup>20,26,27</sup> Whatever the condition, the basal amount of energy required for maintaining lean functional body mass, i.e. resting energy expenditure (REE), is incompressible. Providing a little more energy to enable movement constitutes isocaloric or isoenergetic feeding, though there is no clear definition of this feeding in the literature.<sup>20</sup> Based on indirect calorimetric determinations and animal data, isocaloric feeding however may be defined as the delivery of 110-130% of REE determined in the resting patient, whereas hypocaloric feeding delivers 0.5-0.9 times the REE and hypercaloric feeding delivers

1.5 times the REE.<sup>20</sup> In resting conditions, 60-70% of REE is devoted to the functioning of vital organs (brain, heart, liver, kidneys). The metabolic activity of these vital organs is considerable: 400-600 kcal/day in the myocardium, 400 kcal/day in the kidney, and 200-250 kcal/day in the brain and liver.<sup>28</sup> This contrasts with the low metabolic activity of adipose tissue (about 5 kcal/kg per day) and the variable activity of skeletal muscle (10-15 kcal/kg per day in resting conditions).<sup>20</sup>

Several decades have passed since early pioneers in the field of surgical metabolism such as Kinney et al.<sup>29</sup> first definitively demonstrated that extensive burns elicit a pronounced metabolic response accompanied by a dramatic increase in the basal metabolic rate.<sup>2,30</sup> It soon became clear that patients with severe burns required caloric deliveries above basal requirements to meet increased energy expenditures.<sup>3,31</sup> The severity of injury and the importance of stress hormone and inflammatory mediator release, fever, organ failure, nutrition and supportive treatments have all been shown to influence the resting metabolic rate.<sup>20,32</sup> Catabolism does not develop in patients with burns in less than 40% TBSA, however, while patients with burns in more than 40% TBSA always experience catabolism.<sup>33</sup> In addition, insufficient pain control may jeopardize other efforts to reduce REE.<sup>20</sup> Global hypermetabolism is also associated with a progressive decline of host defences that impairs the immunological response. It is also associated with other considerable clinical manifestations, including delayed wound healing, fever, sepsis, tachycardia, cardiac ischaemia, derangement in hepatic protein synthesis, generalized muscle weakness and muscle protein catabolism with loss of lean body and muscle mass that prolongs the period of rehabilitation, and potential death.<sup>2,30,34-38</sup>

Although, stress response after burn injury is similar to any major trauma, severe burns are characterized by an impressive hypermetabolic response that is more severe and sustained than any other form of trauma.<sup>14</sup> Early studies demonstrated a relationship between the percentage of TBSA burned and energy requirements.<sup>1</sup> Subsequent investigations have consistently confirmed that severe burn injury nearly doubles REE and that burn-related hypermetabolism results in a loss of body fat stores and a loss of visceral and structural protein mass.<sup>39</sup> Interestingly, resting metabolic rates in burn patients increase in curvilinear fashion, ranging from near normal for burns of less than 10% TBSA to 180% of the basal rate in burns in more than 40% TBSA during the acute phase at a thermally neutral temperature (33° C), 150% at full healing of the burn wound, 140% at 6 months after the injury, 120% at 9 months after injury, and 110% at 12 months.<sup>13,14,40</sup> In paediatric patients with >40% TBSA burn, the resting metabolic rate increased to ranges between 160% and 200%.<sup>13</sup> The molecular mechanism of the hypermetabolic response to burn injury is not fully understood. It appears that ap-

proximately 60% of the increased metabolic response is attributable to an increased protein synthesis, gluconeogenesis, urea production, and substrate cycling.<sup>39</sup> The remaining 40% may be attributable to altered Na<sup>+</sup>-K<sup>+</sup>-AT-Pase activity and proton leakage across the mitochondrial membrane.<sup>39</sup>

At this time, there are insufficient data on protein, fat, and carbohydrate requirements in traumatically injured or burned patients to provide any Level I recommendations.<sup>1</sup> For this reason, guidelines can only be applied broadly to patients.<sup>1</sup> Glucose is an important energy source to promote the sparing of lean body mass in patients with burns, although there are limits to the amount of glucose that injured patients can metabolize.<sup>3</sup> Excessive carbohydrate administration results in hyperglycaemia and increased carbon dioxide production causing hepatic lipogenesis and liver function abnormalities.<sup>3</sup> Optimal carbohydrate delivery has been determined as 5 mg/kg body weight/min of glucose.<sup>41</sup> Similarly to all critically ill patients, adequate protein intake is required and is crucial to maintain lean body mass.<sup>14,42</sup> Protein requirements are largely established based on reports from the early 1980s presenting dose ranges believed to be appropriate - most of these reports are however Class II studies.<sup>1</sup> It has been claimed that in burns greater than 10% TBSA, a nonprotein calorie-to-nitrogen ratio of 100:1 is required to achieve a positive nitrogen balance.<sup>43,44</sup> Due to the fact that there is an increased oxidation rate of amino acids in burn patients at rates that are 50% higher than rates in healthy fasting individuals<sup>14,42</sup> and because of increased protein demand for gluconeogenesis in the acute phase, for the healing of extensive wounds and for replacement of nitrogen losses, more protein than the daily recommended allowances is needed.<sup>3</sup> The protein requirement is increased to 1.5-2.0 g/kg per day in severely burned patients.<sup>14,42</sup> It must also be noticed that in critically ill septic and trauma patients, the achievement of a positive nonprotein energy balance or total energy balance does not prevent a negative nitrogen balance.<sup>20,22</sup> Current recommendations are 20% of total calories as protein.<sup>3,31</sup> Fat distribution of 30% of total calories is commonly used for severely burned patients,<sup>3,45</sup> though diets containing 15% to 20% of non-protein calories as fat appear to be optimal.<sup>46</sup> Large amounts of fat, especially omega-6 fatty acids, can have an immunosuppressive effect by stimulating the release of arachidonic acid, which leads to the formation of prostaglandins depressing delayed cell-mediated hypersensitivity, lymphocyte proliferation, and natural killer-cell function.<sup>3,31</sup> Although specific vitamin and mineral requirements of patients with severe burns have not been established, recommendations for micronutrient supplementation for minor and major burns have been published. Provision of at least the recommended daily allowance is advocated.<sup>3</sup>

### Metabolic and hormonal changes following severe burn injury

Severe dermal burns are associated with increased levels of catecholamines and catabolic hormones<sup>1,2,47</sup> and are known to induce a systemic inflammatory response syndrome (dermal inflammatory and pro-apoptotic signalling).<sup>2,48-50</sup> In the absence of inhalation injury, the burn wound itself is the triggering source of systemic inflammation via liberation of a plethora of potentially deleterious pro-inflammatory mediators and attraction/activation of neutrophils.<sup>2,38,51</sup> The inflammatory response is correlated with a high risk of end-organ failure, increased risk of infection, sepsis, and immunosuppression.<sup>2,48-50</sup> Moreover, severe thermal injury is associated during the early shock states with decreased oxygen consumption, glucose tolerance, and cardiac output. These metabolic variables gradually increase during the first five days after injury.<sup>14</sup> Elevated energy expenditure closely matches also increased substrate oxidation, which results from significant aberrations in the major ATP consumption pathways. In severely burned patients these pathways control increased protein turnover, enhanced gluconeogenesis, elevated urea production, and substrate cycling. Approximately 60% to 70% of increased total energy expenditure results from ATP consumed by these processes, whereas 40% occurs from uncoupled reactions in cellular membranes and proton leakage in mitochondria.<sup>14,39</sup>

Glucose-dependent tissues are normally assured an energy source by increased hepatic gluconeogenesis and peripheral resistance to insulin.<sup>16</sup> During the "flow" phase of the early post-burn hypermetabolic response there are increased serum fasting glucose and insulin levels, reduced rates of glucose disappearance (insulin resistance), and an enhanced total glucose delivery to peripheral tissues.<sup>14</sup> Observed insulin resistance is associated with decreased insulin signalling. Residues on insulin receptor substrate-1 (relatively proximal in the signal transduction sequence) are phosphorylated, thus rendering the signal less robust.<sup>16</sup> The development of hyperglycaemia in severely burned patients is not surprising, due to dramatic increases in gluconeogenesis and glucose substrate cycling.<sup>16</sup> Lactate, produced by anaerobic oxidation of glucose in the wound bed, is recycled to the liver to produce glucose via gluconeogenic pathways.<sup>52</sup> Furthermore, three-carbon amino acids (mainly alanine), released as the result of continuing degradation of peripheral muscle, are also used as a substrate for the increased gluconeogenic drive. As a result of these changes in metabolic pathways, lean muscle protein breakdown is amplified in both the acute and the convalescent phases of the response to burn injury.<sup>14,53</sup>

While hyperglycaemia is beneficial, up to a point, numerous studies have shown that in the intensive care unit (ICU) and in burn patients it is associated with a worse

outcome, impaired immune function, poor wound healing, and exacerbation of protein muscle catabolism; also, glucose oxidation remains limited.<sup>14,16,52</sup> The greatly increased glucose flux is almost entirely directed to the burn wound, where glucose is consumed during anaerobic metabolism by fibroblasts and endothelial and inflammatory cells.<sup>14,52</sup> Also associated with hypermetabolism in severe burns are increases in substrate cycling, particularly of glucose and fatty acids. A substrate cycle exists when opposing, nonequilibrium reactions catalysed by different enzymes are operating simultaneously, with at least one of the reactions involving the hydrolysis of ATP. Thus, a substrate cycle both liberates heat and increases energy expenditure without any beneficial effect. In severe burns, the total rates of triglyceride-fatty acid and glycolytic-gluconeogenic cycling without effective product are 450% and 250%, respectively, over normal controls.<sup>14,16</sup> This futile substrate cycling contributes to increased thermogenesis, which in turn elevates core temperatures to 2 °C greater than normal in these patients.<sup>14,54</sup>

### Assessment of energy and substrate requirements

Accurate estimation of metabolic needs and energy requirements in burn patients is of paramount importance but it is difficult to determine because of many factors.<sup>1</sup> Undoubtedly, there are advantages to the use of easily assessed variables.<sup>55</sup> Early studies have demonstrated a relationship between the percentage of TBSA burned and energy requirements.<sup>1</sup> The well-known, frequently used Curreri formula ( $25 \times \text{body weight [kg]} + 40 \times \text{percentage BSA burned}$ ) proposed in the late 1970s is a simple prediction of daily metabolic needs based on easily attainable information.<sup>18,55-57</sup> At present the "gold standard" for determining the caloric needs of patients with traumatic injuries is to measure their energy expenditure with indirect calorimetry, which provides a relatively inexpensive, portable method of assessing the need for nutritional support.<sup>18,58</sup> By measuring oxygen consumption ( $\text{VO}_2$ ) and carbon dioxide production ( $\text{VCO}_2$ ), REE can be calculated using the abbreviated Weir equation:  $\text{REE} = [3.9 (\text{VO}_2) + 1.1 (\text{VCO}_2)] \times 1.44$ .<sup>1</sup> Dietary intake is adjusted accordingly to match the calculation.<sup>18,58</sup> A later study using indirect calorimetry showed, however, that the Curreri formula is still a good approximation of patient needs<sup>59</sup> and that calorimetry measurement alone is still not the answer to all metabolic questions since it is only a snapshot measurement in time.<sup>18,60</sup>

Energy expenditures actually rise from the time of admission through the 10th to 20th post-burn day; they decline thereafter but remain elevated at the time of discharge.<sup>1</sup> It should also be mentioned that the caloric requirements of the burn patient fluctuate in the course of burn wound healing and that, even in the absence of a

demonstrated relationship between the percentage of burn wound remaining open and energy expenditure, a burn patient's caloric needs fluctuate from day to day depending on other factors, such as temperature, activity level, degree of anxiety, pain control, ventilator dependency, caloric intake, the presence or absence of sepsis, and other yet-to-be defined factors. Therefore, providing the same caloric requirement to burn patients over time exposes them to the risk of overfeeding or underfeeding.<sup>1</sup>

Several methods have been used to estimate patients' energy requirements as an alternative to measuring actual energy requirements with indirect calorimetry.<sup>1</sup> Since the description of the Curreri formula, which seems to consistently overestimate actual energy expenditure, many formulas have been proposed as more accurate predictors of burn patients' caloric requirements. Some formulas include a factor for TBSA burned, as in the Curreri formula, and are based on the patient's TBSA and/or TBSA burned, such as the Toronto formula, which matches the measured energy expenditure very closely and, with the addition of a factor of activity for 24-h energy expenditure, can be used to supplement individual burn patients with nutrition accurately.<sup>61-63</sup> Other formulas do not account for the TBSA burned and are based on calculations of basal energy expenditure (BEE), as determined by the Harris-Benedict equation, which takes into account the patient's age, sex, height, and weight. Energy expenditure in burn patients exceeds that predicted by the standard Harris-Benedict equation by 132%. This discrepancy can be corrected by multiplying the calculated BEE by factors for the degree of stress (injury) and for the level of patient activity. The Harris-Benedict-derived BEE calculations are widely used at present; however, they underestimate by 23% actual energy expenditure for second- and third-degree burns ranging between 10% and 75% TBSA, while the Curreri formula overestimates energy expenditure by 58%.<sup>1,57,64</sup>

Despite the many published studies that claim the superiority of a particular formula over the Curreri formula in the prediction of burn patients' energy requirements, this formula remains that most commonly used.<sup>1</sup> A computer program has even been developed that automates the process of calculating caloric requirements in burn patients according to the Curreri formula as well as the amount of glucose, fat, and proteins in grams to meet their caloric requirements.<sup>43</sup> Indirect calorimetry is infrequently carried out on a routine basis and it appears that there are no differences in patient outcome when calories are provided on the basis of direct measurement of energy expenditure or on the basis of a mathematical formula.<sup>1</sup> Although many of the mathematical calculations provide accurate estimates, many do not and can lead to overfeeding, with all its inherent complications.<sup>1</sup> Regardless of whether the Curreri formula is used or the BEE multiplied by an activity fac-

tor and/or a stress factor, it is frequently difficult, if not impossible, for a patient to ingest the estimated requirement of calories.<sup>1</sup> Moreover, it seems unwise to attempt to achieve these high caloric loads by supplementing enteral nutrition with parenteral nutrition - this may result in significantly higher mortality and greater depressions in T-helper/suppressor ratios.<sup>1</sup> However, the high degree of variability in energy requirements for hypermetabolic burn patients limits the value of standardized formulas for estimating individual nutritional needs.<sup>65</sup> It should always be remembered that the formulas described provide at best only an estimate of an individual patient's initial energy and substrate needs, that these requirements will vary throughout the course of the illness and recovery,<sup>1</sup> and that there is undoubtedly an obligatory relative inaccuracy in using any static formula to predict burn patients' dynamic energy needs.<sup>65</sup> It is unlikely that there is an ideal energy or substrate formula that will perform better than those currently in use. However, more reliable and easier-to-use means of measuring energy expenditure and substrate use would have significant advantages over the current state of technology with indirect calorimetry.<sup>1</sup>

#### **Starvation, hypocaloric feeding, hypercaloric feeding, and metabolic adaptation**

Generally speaking, hypocaloric nutrition, although frequent in both ICUs and in burn units, is not deliberate.<sup>66,67</sup> Often observed in critically ill patients, particularly during the first 5-7 days after admission, it is usually due to the difficulty of rapidly supplying the necessary volume of enteral feeding.<sup>20,66,67</sup> Nursing practices also contribute to unintentional hypocaloric feeding.<sup>68</sup> Fortunately, the body has a normal adaptive response and can reduce energy expenditure to some extent.<sup>20,69</sup> However, nobody yet knows exactly how long hypocaloric feeding can be tolerated in acutely ill patients. Clearly, the tolerable length of limited intake will depend on the severity of the patient's condition.<sup>20</sup> Prolonged fasting and underfeeding are deleterious, even in healthy subjects, and are not tolerated for more than a few days without deleterious side effects either by healthy subjects or by sick patients. The resulting malnutrition causes erosion of lean body mass and is a recognized cause of prolonged hospital stay.<sup>20,70</sup> Even for elective scheduled surgery, pre-operative fasting is deleterious. It increases insulin resistance and causes negative nitrogen balances, with deleterious effects on muscle function.<sup>71</sup> By contrast, pre-operative carbohydrate administration and early post-operative feeding may improve muscle function, maintain nitrogen balance, and improve tolerance to enteral feeding without any insulin requirements.<sup>72</sup>

Metabolic alterations and adaptations that occur during starvation are: 1. tipping of the energy source from glucose to fatty acids in the majority of organs; 2. adap-

tation of the Cori cycle; and 3. the brain's ability to use keto acids to spare glucose. Proteins are the precious core that is preserved by these three mechanisms.<sup>20,73</sup> However, achievement of a positive non-protein energy balance or a total energy balance in critically ill, septic, and traumatized patients does not prevent a negative nitrogen balance.<sup>20,22</sup> Strange as it may be, there is growing evidence in the literature that a short period of restricted intake might be beneficial and that delivering hypercaloric nutrition to critically ill patients may be deleterious: thus overfeeding should be prevented.<sup>74</sup> It has been shown that partial and complete starvation with restricted nutrient intake may have beneficial effects on animal life span, the development of degenerative disease, autoimmune processes, renal injury, susceptibility to infection, and post-infection survival rate.<sup>20,75</sup> On the other hand, overfeeding is deleterious and causes a series of side effects such as hyperglycaemia, fatty liver, higher rates of infectious complications, and ultimately increased mortality.<sup>20</sup> Aggressive high-calorie feeding with a combination of enteral and parenteral nutrition is also associated with increased mortality.<sup>24</sup> Enteral feeding beyond the body's energy expenditure (20-40% above REE) does not improve lean body mass. On the contrary it is associated with complications such as fatty liver.<sup>34</sup> Recognition of the adverse effects of overfeeding has stimulated an effort to tailor nutritional support to patients' precise needs.<sup>65</sup> Most authors now recommend adequate calorie intake via enteral feeding, avoiding overfeeding.<sup>42</sup>

Despite the fact that there is no solid evidence that hypocaloric feeding is deleterious in the first days after ICU admission, many recent studies show that there is a direct association between negative energy balances and septic or nonseptic complications during the first week and that these are associated with poor ICU and hospital outcome.<sup>20</sup> The comparison of various levels of fasting has shown that the duration of fasting and the severity of illness are the main determinants of the deleterious effects that may arise.<sup>75</sup> A cumulated negative energy balance greater than minus 10,000 kcal at the end of the first week is usually associated with an increasing number of complications such as infections and days of antibiotic treatment, as also with the duration of mechanical ventilation and ICU stay; the more negative the balance, the higher the number of complications.<sup>67</sup> Moreover, delaying initiation of nutritional support exposes patients to energy deficits that cannot be compensated later on.<sup>20</sup>

### **Route and timing of nutritional support**

Nutritional supply undoubtedly is of fundamental importance in the treatment of critically ill patients.<sup>76</sup> However, different feeding levels have definite different systemic consequences.<sup>22</sup> It has been reported that patients with 40% TBSA treated with vigorous oral alimentation

alone can lose a quarter of their pre-admission weight within three weeks after injury.<sup>14,77</sup> Other reports on continuous enteral or parental nutrition in adults delivering 25 kcal (0.105 MJ)/kg per day plus 40 kcal per percentage burn area per day or 1800 kcal (7.56 MJ)/m<sup>2</sup> per day plus 2200 kcal/m<sup>2</sup> of burn area per day, on the other hand, describe the successful maintenance of total body weight in burn patients.<sup>47,56,78</sup> Regardless of these controversial reports, burn victims suffer an obligatory loss of lean body mass that feeding or overfeeding will not prevent.<sup>65</sup>

The first suggestion that route and type of nutrition influence the clinical outcome of severely burned patients was made by Alexander et al.<sup>1,79</sup> Enteral nutrition support seems to be the best feeding method for patients who are unable to achieve an adequate oral intake to maintain gastrointestinal motility and function and reduce translocation bacteraemia and sepsis.<sup>14,25</sup> It is preferable and superior to parenteral nutrition, which is reserved to severely injured (burn/trauma) patients with enteral feeding intolerance or prolonged ileus.<sup>14,21,80,81</sup> Failure to maintain enteral nutrition is also associated with immunological changes and impairment of the gut-associated immune system.<sup>82</sup> Moreover, feeding by the intravenous route or giving crystalline amino acids instead of intact protein does not prevent intestinal mucosal atrophy, nor does it prevent the hypermetabolic response.<sup>79</sup> The relative superiority of enteral over parenteral nutrition in the trauma patient should not however be used as an excuse for delaying appropriate nutritional support. Many trauma patients are hypermetabolic, and depletion of nutrient stores proceeds more rapidly in cases of total starvation than in healthy adults. The functional consequences of total or partial starvation thus evolve more rapidly in stressed and catabolic patients than in healthy individuals. For these reasons, most investigators recommend the achievement of nutritional support goals by post-injury day 7 in severely injured patients, whether by enteral or parenteral means or by some combination of the two.<sup>1</sup>

Questions remain regarding the optimal method and timing of enteral nutritional support.<sup>83,84</sup> Recently published reviews<sup>84</sup> advocate the notion of early initiation of enteral feeding to attenuate the catabolic response and decrease muscle wasting after thermal injury.<sup>23</sup> Although the superiority of enteral over parenteral nutrition for burn patients appears to be well established, controversy continues over the optimal route of delivery for enteral nutritional support. Some experts believe that intragastric feeding is more difficult than feeding with intestinal tubes, while others deny that any difference exists.<sup>65</sup> Intragastric feeding should be started as soon as possible after admission, because delayed enteral feeding (> 18 h) results in a high gastroparesis rate.<sup>1</sup> It has been reported that the use of early nasogastric tube insertion, with the charting out of daily calorie intake and the use of low-cost feeds consistent with local dietary habits, leads to a significant decrease in the av-

average number of days of hospitalization and the number of procedures in 20-39% TBSA burns and to a significant decrease in mortality, the average number of days of hospitalization, and the number of surgical procedures in 40-59% TBSA burns.<sup>30</sup> Early enteral feeding also has beneficial effects on the improvement of renal function, as demonstrated experimentally, which may be related to the increase in splanchnic blood flow, the decrease in the translocation of gut-originated endotoxin, and the release of inflammatory mediators.<sup>86</sup> When diets were started within 15 h, the nutritional goals were reached in 82% of the patients within 72 h whereas, when feeding was delayed for 18 h or more, the majority of patients failed to achieve their goals. Moreover, tolerance of intragastric feedings was seen in more than 90% of patients if feeding started within 6 h of the burn injury.<sup>1</sup> In contrast, however, intraduodenal feeding, if started within 48 hrs, is also well tolerated, with rare episodes of distension, reflux, or diarrhoea.<sup>1</sup> It is not however certain that small intestine tube feeding (nasoduodenal or nasojejunal tube) is manifestly superior to gastric feeding, with respect to both clinical outcome and risk.<sup>21,84</sup> At present, the successful administration of enteral feeding of any type, especially in critically ill patients, continues to be complex and labour-intensive. Surgeons who manage these patients need to individualize route, rate, and the use of adjunctive methods and to continue to monitor patients carefully if they are to ensure success and avoid complications.<sup>65</sup>

As evidenced by a series of laboratory experiments, it seems that the decrease in metabolic response secondary to feeding by the enteral route immediately after burn injury is due to the preservation of the gastrointestinal barrier, preventing translocation of intestinal endotoxin and bacteria.<sup>76,87</sup> However, patients who are incompletely resuscitated should not have direct small bowel feeding instituted because of the risk of gastrointestinal intolerance and possible intestinal necrosis.<sup>1</sup> In some studies prokinetic

agents such as erythromycin and metaclopramide have been used to enhance gastric tolerance of enteral nutrition.<sup>64</sup> Although providing early nutritional support to burn patients has a number of theoretical advantages, including increased caloric intake,<sup>88</sup> improved bowel mucosal integrity,<sup>89</sup> and partial abatement of the hypermetabolic response,<sup>23,90</sup> it is unclear whether it results in an improvement in clinical outcome measures, such as decreased length of stay, decreased incidence of infections, or decreased mortality.<sup>21,25,36,37</sup> Nor is it clear that aggressive, early enteral nutritional support after burn injury is as safe and easy as has been previously reported.<sup>21,91</sup> Similarly, the question of whether early enteral feeding influences or decreases hypermetabolism also remains uncertain.<sup>21,25,37</sup> Recent studies in a variety of patient populations suggest that early nutritional support may not only be unnecessary<sup>92</sup> but may lead to more complications, including pulmonary aspiration<sup>83,93</sup> and intestinal necrosis.<sup>21,37,94</sup>

One potential disadvantage regarding the enteral approach to nutrition is the concern that adequate amounts of protein and calories cannot be delivered via this route because of frequent interruptions in feeding resulting from multiple operative procedures. Most patients in North American burn centres are given nothing by mouth for at least 6 to 8 h before surgery.<sup>95,96</sup> It has been shown however that, in selected patients, enteral feeding can be safely administered up to the time of transport to the operating room.<sup>1</sup> Moreover, the feasibility and safety of continuing enteral feeding throughout operative procedures in a very select group of burn patients with enteral access established beyond the pylorus and airway access obtained via an endotracheal tube or tracheostomy have also been demonstrated.<sup>1,97</sup> Round-the-clock feeding without interruption for procedures has now been achieved.<sup>18</sup> This approach facilitates delivery of greater amounts of protein and calories without an increase in peri-operative aspiration events<sup>1</sup> - but is this the best possible method?<sup>18</sup>

**RÉSUMÉ.** Les grands brûlés constituent un groupe de patients critiquement malades difficiles à traiter et exposés à un stress physiologique extrême et à une réaction métabolique systémique dévastatrice. La quantité augmentée d'énergie qu'il faut utiliser pour affronter cette condition requiert la mobilisation de grandes quantités de substrat provenant des réserves de graisse et du muscle actif pour la réparation et pour carburant, ce qui mène au catabolisme. La réponse métabolique peut durer jusqu'à neuf mois et même un an après la brûlure, associée à un processus altéré de la guérison des lésions, des risques d'infection augmentés, l'érosion de la masse corporelle maigre, une rééducation gênée et un retard dans la réintégration dans la société des patients non décedés. L'inversion de la réponse hypermétabolique, moyennant la manipulation de l'état physiologique et biochimique du patient, obtenu grâce à l'administration de substances nutritives spécifiques, de facteurs de la croissance et d'autres agents, souvent en doses pharmacologiques, commence à émerger comme composante essentielle de l'état de l'art pour ce qui concerne la gestion des brûlures sévères. Le support nutritif entéral précoce, le contrôle de l'hyperglycémie, le blocus de la réaction des catécholamines et l'emploi de stéroïdes anaboliques ont été proposés pour atténuer l'hypermétabolisme ou pour éteindre le catabolisme associé aux brûlures sévères. Les Auteurs de la présente étude ont passé en revue la littérature relative pour ce qui concerne les mesures thérapeutiques nutritionnelles et métaboliques proposées dans le but de déterminer les pratiques meilleures sur la base de l'évidence. Malheureusement, l'état présent des connaissances ne permet pas la formulation de lignes directrices bien définies. Il est seulement possible d'indiquer à grands traits des tendances générales qui certainement auront des applications pratiques mais surtout dicteront les recherches futures dans ce secteur.

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Part 2 of this review will be published in the next issue of the journal.

## **G. WHITAKER INTERNATIONAL BURNS PRIZE-PALERMO (Italy) Under the patronage of the Authorities of the Sicilian Region for 2009**

By law n. 57 of June 14th 1983 the Sicilian Regional Assembly authorized the President of the Region to grant the Giuseppe Whitaker Foundation, a non profit-making organization under the patronage of the Accademia dei Lincei with seat in Palermo, a contribution for the establishment of the annual G. Whitaker International Burns Prize aimed at recognizing the activity of the most qualified experts from all countries in the field of burns pathology and treatment.

Law n. 23 of December 2002 establishes that the prize becomes biannual.

The next prize will be awarded in 2009 in Palermo at the seat of the G. Whitaker Foundation.

The amount of the prize is fixed at Euro 20,660.00.

The Adjudicating Committee is composed of the President of the Foundation, the President of the Sicilian Region, the Representative of the National Lincei Academy within the G. Whitaker Foundation, the Dean of the Faculty of Medicine and Surgery of Palermo University or his nominee, a Representative of the Italian Society of Plastic Surgery, three experts in the field of prevention, pathology, therapy and functional recovery of burns, the winner of the prize awarded in the previous year, and a legal expert nominated in agreement with the President of the Region as a guarantee of the respect for the scientific purpose which the legislators intended to achieve when establishing the prize.

Anyone who considers himself to be qualified to compete for the award may send by **January 31st 2009** his detailed curriculum vitae to: Michele Masellis M.D., Secretary-Member of the Scientific Committee, G. Whitaker Foundation, Via Dante 167, 90141 Palermo, Italy.